Cont E46a 47

SphI
5' GGCGGCATGCGGCGGTTCCT3' (SEQ ID NO: 90)

NheI HpaI
5'AAGCTAGCGGTTCGCCGGGCGCCGCTTCGTTGGTCCGCGCGCGGGTTAAC3'(SEQ ID NO: 91)

E48 (Page 117, Line 34) The following complementary synthetic oligonucleotides were synthesised so as when annealed, they would have the necessary pattern at the 5' and 3' ends that is produced by the action of HpaI and NheI respectively
5'AACCCGCGCGCGGACCAACGAAGCGGCGCCCGGCGAACCG3'(SEQ ID NO: 92)
5'CTAGCGGTTCGCCGGGCGCCGCTTCGTTGGTCCGCGCGCGGGTT3'(SEQ ID NO: 93)

In the Claims:

Amend claims 24, 27, 29, 31-34 and 37-39 as follows:

E49 24. (Amended) A hybrid PKS gene according to claim 2, wherein said at least one first nucleic acid portion encodes a loading module together with only the ketosynthase ("KS") domain of the extension module, which is homologous to said loading module.

E50 27. (Amended) A hybrid PKS gene according to claim 26, wherein said loading module is the loading module of the avermectin-producing PKS of streptomyces avermitilis.

E51 29. (Amended) A hybrid PKS gene according to claim 1, including a nucleic acid sequence encoding a chain terminating enzyme other than thioesterase.

31. (Amended) A nucleic acid sequence encoding a gene according to claim 1 operably linked to a PKS type II promoter.

32. (Amended) A nucleic acid sequence according to claim 31 further comprising the natural activator gene for said promoter.

33. (Amended) A nucleic acid sequence according to claim 31, wherein the promoter is act I of S. coelicolor.

34. (Amended) A nucleic acid sequence according to claim 32, wherein the promoter is act I of S. coelicolor.

37. (Amended) A transformed microorganism containing a gene according to claim 1 and able to express a polyketide synthase encoded thereby.

39. (Amended) A method of making a polyketide by culturing the microorganism of claim 37.

Please add new claims 44-58 as follows:

44. A hybrid PKS gene according to claim 1, wherein said first nucleic acid portion encodes at least a loading module which comprises an acyltransferase and an acyl carrier protein, and said second nucleic acid portion encodes at least one extension module.

45. A hybrid polyketide synthase ("PKS") gene comprising a first nucleic acid portion encoding a plurality of naturally contiguous modules of a first type I PKS whereof nucleic acid encoding a first combinatorial module portion, said first combinatorial module portion

being a portion extending from a first point within a first one of said naturally contiguous modules to a second point equivalent to said first point in a second one of said naturally contiguous modules so that it comprises the part of said first module downstream of said first point and the part of said second module upstream of said second point, linked optionally via one or more third modules, has been replaced by a second nucleic acid portion which encodes a second combinatorial module portion extending between corresponding first and second points so that it comprises a downstream part of a fourth module and an upstream part of a fifth module, linked optionally via one or more sixth modules; said fourth, fifth and sixth modules being heterologous to said first type I PKS.

46. A hybrid PKS gene according to claim 1, wherein said at least one second nucleic acid portion comprises a portion which replaces a nucleic acid portion of the gene for said first type I PKS which encodes an extension module which would contribute to a polyketide being synthesised by the PKS a first ketide unit; said portion of said at least one second nucleic acid portion encoding an extension module which is adapted to contribute to a polyketide being synthesised by the PKS a second ketide unit which differs from said first ketide unit in at least one of the characteristics selected from the group consisting of oxidation state, stereochemistry, and substitution pattern.

47. A plasmid comprising a gene according to claim 1.

48. A transformant microorganism which has been transformed so that it harbours a plasmid according to claim 47.

49. A transformant microorganism according to claim 48 in which said plasmid replicates autonomously.

50. A plasmid comprising a gene according to claim 1 and an int sequence whereby it is adapted to integrate into a specific attachment site (att) of a host's chromosome.

51. A method of producing a transformant microorganism comprising the steps of:

(a) producing a plasmid which comprises donor DNA which is a gene according to claim 1, and

(b) transforming with said plasmid a microorganism having a chromosome including DNA which undergoes homologous recombination with said plasmid to integrate said gene into the chromosome.

52. A method of producing a transformant microorganism comprising the steps of:

(a) producing a plasmid which comprises donor DNA which encodes at least one domain of a first type I PKS;

(b) transforming with said plasmid an organism having a chromosome including PKS genes comprising at least one second type I PKS gene which is heterologous to said first PKS, said plasmid and chromosome being mutually adapted so that said donor DNA is integrated into the chromosome so as to form with a portion of said second type I PKS gene a hybrid PKS gene encoding at least one domain of said first type I PKS and at least one domain of said second type I PKS.

53. A method according to claim 51, wherein said plasmid includes an int sequence and said chromosome has an att site for integration of the plasmid at a location suitable for producing said hybrid PKS gene.

54. A hybrid PKS gene according to claim 1, wherein said first type I PKS naturally includes a thioesterase as a chain terminating enzyme, and wherein said hybrid gene includes a nucleic acid sequence encoding the enzyme from the rapamycin system which, in that system, effects connection of the polyketide chain to an amino acid.

55. A transformed prokaryotic organism containing a gene according to claim 1 and operable to express a polyketide synthase encoded thereby.

56. A transformed microorganism which naturally expresses a polyketide synthase and which contains as a result of its transformation a gene according to claim 1 and is operable to express a polyketide synthase encoded thereby.

57. A method of making a polyketide by culturing the organism of claim 55.

58. A method of making a polyketide by culturing the microorganism of claim 56.

Please cancel claims 28, 30, 38, and 40-43 without prejudice.

A marked-up version of the amended specification and claims 24, 27, 29, 31-34, 37 and 39 is attached.

REMARKS

The September 11, 2001 Official Action and the references cited therein have been carefully considered. In view of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of this application are respectfully requested.